TABLE I. Immunologic Abnormalities Amongst Three Study Groups

	HIV positive symptomatic (N = 12)	HIV Positive asymptomatic (N = 24)	HIV negative (N = 36)	
Absolute lymphopenia	4	0	0	<0.0001*
CD4+ lymphopenia	8	0	1	<0.0001*
CD4:CD8 ratio <1	7	2	1	<0.001*
Cutaneous anergy	10	5	2	<0.001*
Hypergammaglobulinemia (Ig G, M, and A)	9	23	33	NS**

*Significant difference and **NS, no significant difference, in HIV positive symptomatic children compared to HIV positive asymptomatic and HIV negative children.

2. T-helper (CD4+) cell count
3. The ratio of T helper and T suppressor (CD8+) cells (CD4/CD8 ratio)
4. Quantitative Ig G, M, and A levels
5. Delayed cutaneous hypersensitivity testing using "multitest CMI" (Institute Merieux, France) against a battery of recall antigens.

Immunologic status of seropositive children was compared with 36 age-matched HIV negative thalassemics (Table I). Three groups of children were defined: (1) seropositive symptomatic with acquired immuno deficiency syndrome (AIDS), (2) seropositive symptomatic, and (3) seronegative control. Statistical analysis was by Kruskal-Wallis test for one way analysis of non-parametric values [3].

Thirty-six of the thalassemic children (8.9%) were found to have antibodies against HIV-I and 12 of these had AIDS. The clinical manifestation included prolonged diarrhoea (8 cases), oropharyngeal andidiaisis (6 cases), bleeding diathesis (6 cases), alopecia (4 cases), pneumocystis carinii pneumonia (2 cases), and lymphadenopathy (2 cases). This symptomatic group was also severely immunologically compromised (Table I). The 8.9% incidence of HIV-I seropositivity in thalassemic children seen here is much higher than the incidence of 1% reported in similar studies [4]. The clinical features of children with AIDS were nevertheless fairly consistent with those found in literature [5]. Patients receiving multiple transfusions of blood are likely to have immunologic alterations independent of HIV infection [6]. This observation might be attributed to repeated transfusion-induced antigenic simulation which in turn results in derangement of the immune system. A battery of laboratory tests is therefore necessary to assess immunodeficiency after multiple blood transfusion. (Table I). Such tests are also useful in identifying the co-relation between clinical manifestation and defecient immunological status in HIV-I seropositive patients and in early recognition of the severity of transfusion-acquired HIV-I disease.

Our findings suggest that the growing incidence of transfusion associated HIV-1 infection in Indian children is becoming a major public health hazard. This is mainly because of unscrupulous professional donation of blood as well as defecient screening of blood products from those donors. This report also emphasizes the serious potential of transmission of HIV-I infection in an unscreened blood transfusion service and the need to incite statutory screening of all blood products.

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References

1. De M, Banerjee D, Chandra S: HBV and HIV seropositivity in multitransfused hemophiliacs and thalassemics in Eastern India. India J Med Res (A) 91:63–66, 1990.
2. Donegan E, Stuart M, Niland JC: Infection with human immunodeficiency virus type 1 among recipients of antibody-positive blood donations. Ann Int Med 11:7–9, 1990.
3. Dawson-Saunders B, Trapp RG: "Basic and Clinical Biostatistics." Ed 2. Connecticut: Appleton & Lange, 1994.
4. Palca J: Infection with selection: HIV in human infants. Science 225:1069–1071, 1992.
5. Pahwa S, Kaplan M, Firkrig S: Spectrum of human T-cell lymphotrophic virus type II infection in children: Recognition of symptomatic, asymptomatic and sero negative patients. JAMA 255:2293–2295, 1986.
6. Hilgartner MW: AIDS in the transfusion recipient. Am J Dis Child 141:194–198, 1987.

Severe Intravascular Hemolysis Associated With Interferon Treatment for Chronic Myeloid Leukemia

To the Editor: α-interferon is now widely used as initial therapy for chronic myeloid leukemia (CML). Hematological complications of interferon treatment include anemia, immune hemolysis, and thrombocytopenia, but to our knowledge nonimmune intravascular hemolysis associated with this therapy has not been described.

A 52-year-old woman was diagnosed with Philadelphia chromosome-positive CML. Treatment with hydroxyurea was commenced, and subsequently peripheral blood stem cells were collected in the recovery phase after cyclophosphamide 5 g/m^2 therapy followed by granulocyte-colony stimulating factor (G-CSF). Two weeks after the stem cell collections, interferon α-2a (roferon), 3×10^6 units/day subcutaneously, was commenced. Hemoglobin (Hb) was 106 g/dl, white cell count (WCC) was 6.2×10^9/l, and platelets were 230×10^9/l. No concomitant medications were administered. Within 4 hr of the first dose of interferon, high fever, rigors, and dark urine developed. These features persisted for 7 days as the daily interferon was continued. At this time, Hb was 63 g/dl. Red cells showed anisopoikilocytosis, but no spherocytes, fragmentation, bite, or blister cells. Reticulocytes were 107×10^9/l (reference range, $60–110 \times 10^9$/l), haptoglobin was <0.06 g/l (range, 0.32–1.92 g/l), lactate dehydrogenase (LDH) was 3,462 IU/l (range, 210–420 IU/l), bilirubin was 41 umol/l (range, 0–19 umol/l), plasma haemoglobin was 972 mg/l (range, 10–40 mg/l), and urine hemoglobin was 2,805 mg/l (range, 1.0–4.0 mg/l). Hemosiderin was not detected in the urine. The direct antiglobulin test for IgG and C3 and Hams acid lysis test were negative. The G6PD screen was normal.

Interferon was discontinued, and 5 units of red cells were transfused. The patient became asymptomatic within 2 days of cessation of treatment. During the next week her Hb value remained stable, with resolution of the indices of hemolysis.

The patient was subsequently given recombinant interferon-α-2b (intron A), 1×10^6 units daily subcutaneously, escalating to 6×10^6 units over a

period of 6 weeks. After 2 months she developed malaise and persistent fever (38–38.5°C) without clinical or laboratory evidence of infection or hemolysis. Interferon-α-2b was ceased with resolution of fever, and she subsequently remains well on hydroxyurea.

A causal association between interferon-α-2a and intravascular hemolysis is suggested by the close temporal relationship of onset of symptoms with the first dose of the drug, the rapid resolution with its withdrawal, and the exclusion of other known causes of intravascular hemolysis. The mechanism by which interferon caused the hemolysis is unclear. Autoimmune hemolysis has been associated with interferon use, but is usually a long-term complication, occurring after a median of 14 months of treatment [1]. In our patient, hemolysis was not obviously immune-mediated, in view of the time course and the inability to detect either IgG or C3 on the red-cell surface. Furthermore, it is difficult to explain hemolysis with interferon-α-2a, but not α-2b, on an immunogenic basis when the biochemical difference between the two is confined to a single amino acid at position 22 [2].

Interferon-α-2a is cloned in an *Escherichia coli* strain, with a final purity >99% [3,4]. While it is theoretically possible that our patient reacted to a "contaminating" *E. coli* protein, we are not aware of reports of intravascular hemolysis associated with biological substances cloned in this way [5].

In the absence of other demonstrable causes, it is likely that the hemolysis was interferon-induced. Nonimmune intravascular hemolysis should be added to the list of potential complications of this drug.

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References

1. Sacchi S, Kantarjian H, O'Brien S, Cohen PR, Pierce S, Talpaz M: Immune-mediated and unusual complications during interferon alfa therapy in chronic myelogenous leukaemia. J Clin Oncol 13:9, 1995.
2. Auteri G: Intron-A. Biotechnology Product Presentation, 1995.
3. Pestka S: The purification and manufacture of human interferons. Sci Am 249:37, 1982.
4. Weibel EK: Biological safety considerations in the production of health care products from recombinant organisms. Biotechnol Adv 12:525, 1994.
5. Hoffmann F, Roferon A: Investigational Drug Brochure, 1993.

Acrocyanosis as a Heralding Sign of Ovarian Benign Teratoma

To the Editor: We report on the uncommon association of cryoagglutinins without hemolysis, which subsided following surgical ablation of an ovarian benign teratoma.

Case Report

A 22-year-old woman was admitted at our Institution for persistent acrocyanosis. Previous vascular (Doppler and capillaroscopy) investigations and present physical findings were unremarkable. Chest X-rays, bone-marrow biopsy, thyroid hormones, erythrocyte sodimentation rate (ESR), C-reactive protein, rheuma test, antinuclear antibody (ANA), immunoglobulin serum levels, lactate dehydrogenase (LDH), aptoglobin, Coombs' test, beta2 microglobulins, serum copper, and serum markers of viral infection were all normal or negative. Cryoagglutinins were 1:2,000. Computed tomography scanning showed the presence of a dermoid cyst 9 × 5 cm, close to her left ovarion. Following surgical ablation of this tumor (the pathological diagnosis being of ovarian benign teratoma), cryoagglutinins and acrocyanosis disappeared. The patient is well 18 months after surgery.

Discussion

The association of autoimmune hemolytic anemia and benign ovarian neoplasm is uncommon in adult patients [1,2]. Our case is exceptional in that the patient, although she had high-titer cryoagglutinins, never became anemic, and there was no evidence of hemolysis.

In our Medline-assisted literature search (for 1987–1995) we were unable to find any similar cases, and we believe ours to be the first report of acrocyanosis heralding an ovarian benign teratoma. We also tend to believe that the resolution of acrocyanosis and the disappearance of cryoagglutinins following surgery rule out a chance association among the three. Indeed, cryoagglutinins and acrocyanosis are known to be causally linked [3], and the development of autoimmune hemolytic anemia is a well-known paraneoplastic sign [4] in a variety of cancers (lymphomas, lung, ovary, tumors of the gastrointestinal tract, etc.). The absence of hemolymphopoietic tissue in the pathological specimen fits with the hypothesis that benign teratoma is not a site of direct cryoagglutinin production but that it serves as a stimulus for such production to occur in normal lymphoid tissue of the host. Once such stimulus was surgically removed, the cryoagglutinins disappeared. Our observation is worth further confirmation: owing to their subclinical manifestation, it is quite conceivable that cryoagglutinin production may have been overlooked in previous cases of teratomas. Accordingly, we propose that cryoagglutinins be systematically sought in benign ovarian teratomas to ascertain the hypothesis that their prevalence is increased in such patients as compared to a control population.

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References

1. Barry KG, Crosby WH: Auto-immune hemolytic anemia arrested by removal of an ovarian teratoma: Review of the literature and report of a case. Am J Med 47:1002–1006, 1957.
2. Levasseur PH, Regnard JF, Paquet JC, Dartevelle PH, Rojas-Miranda A, Merlier M: Anémie hémolytique auto-immune et dysembryome médiastinal chez une enfant de six ans. Exérèse et guérison de l'anémie. Ann Chir 42:170–172, 1988.
3. Rosse W, Bunn HF: Acquired hemolytic anemias. In Isselbacher K, Braunwald E, Wilson, Martin J, Fauci A, Kasper D (eds): "Harrison's Principles of Internal Medicine," Ed 13. New York: McGraw Hill, 1994, pp 1748–1752.
4. Bunn PA Jr, Ridgway EC: Paraneoplastic syndromes. In De Vita VT Jr, Hellman S, Rosenberg SA (eds): "Cancer Principles and Practice of Oncology," Ed 4. Philadelphia: J.B. Lippincott Co., 1993, pp 2047–2053.

Aplastic Anemia During Treatment With Albendazole

To the Editor: Albendazole is a benzoimidazole-carbamate compound whose use is rising in the medical treatment of hydatid disease [1]. Adverse